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NMDA receptor autoimmunity in mania following HSV encephalitis

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Herpes simplex virus (HSV) encephalitis (HSVE) is the commonest cause of death in cases of sporadic encephalitis in humans (Johnston, 1998) with relapse occurring in approximately 12% of patients (Skoldenberg et al., 2006). Whilst commonly attributed to viral reactivation, it is increasingly recognised that a proportion of 'relapses' are due to anti-NMDA receptor encephalitis (NMDARE), a treatable autoimmune disorder caused by IgG autoantibodies against the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor. While the proportion of clinical relapses from HSVE attributable to NMDARE remains unknown, a recent study found 30% of post HSVE patients had anti-NMDA receptor antibodies in serum, or CSF (Pruss et al., 2012). Affective symptoms have been described as a presenting symptom of HSVE, as well as a sequel (McGrath et al., 1997, Leyboldt et al., 2013), although the underlying mechanisms have not been elucidated. We report the case of a manic episode associated with transient NMDA receptor autoimmunity occurring as a sequel to HSVE.

A 37-year-old male with an unremarkable medical history was admitted to hospital with headaches and subsequently suffered a generalised seizure and cardio-respiratory arrest. MRI revealed acute restricted diffusion in the right mesial temporal lobe and a cerebrospinal fluid (CSF) sample was positive for HSV type 1 (HSV-1). He was treated with intravenous acyclovir and discharged with residual symptoms of headache, fatigue and bilateral tremor of the upper limbs.

One month later he was brought back to hospital with a four-day history of paranoia and insomnia. On arrival he was distractible and preoccupied with colours and numbers and highly agitated, requiring intramuscular sedation. Neurological exam revealed gaze impersistence and saccadic intrusion of smooth pursuit, fine tremor with superimposed myoclonic jerks and subtle perioral myoclonus. Neuropsychiatric assessment revealed manic symptoms including social disinhibition, elation, increased self-esteem and tangential thoughts.

Initial blood results revealed elevated C-reactive protein (23 mg/L) and neutrophil count ($7.9 \times 10^9/L$). Serum anti-NMDA receptor antibody using a live cell-based assay was low positive (scoring 1.5 on a 0-4 scale at 1:20 dilution and 0.5 at 1:100 dilution). Serum anti-VGKC and onconeural antibody screen were negative. CSF revealed elevated protein (784 mg/dL) and white blood cells (9 cells/ μ), as well as unmatched oligoclonal bands. A CSF and serum viral screen, which included HSV-1 PCR, was negative.

MRI head revealed signal abnormality, with swelling within the right anteromesial temporal lobe and dorsal frontal lobe extending into gyrus rectus and posteriorly into the ipsilateral parietal and occipital lobes with blurring of grey-white matter differentiation in keeping with recent HSVE. EEG revealed a delta-brush like appearance, a pattern reported to be highly specific for NMDARE (Schmitt et al., 2012).

He was commenced on IV acyclovir, prior to excluding a viral aetiology, thereafter treated with regular clonazepam 1mg BD, leading to partial reduction of his manic symptoms and he was discharged after two weeks. Repeat serum anti-NMDA receptor antibody assay was negative and EEG was normal, whilst MRI showed resolving signal hyperintensity and reduced swelling, with some persisting signal abnormality in the right anteromesial temporal lobe. Repeat neuropsychiatric assessment revealed resolution of manic/psychotic symptoms and cognitive impairment (see figure 1).

The case expands the likely clinical manifestations of post-HSV NMDA receptor autoimmunity, as well as suggesting a plausible explanation for some of the cognitive and affective changes occurring after HSVE.

Evidence supporting the pathogenic relevance of NMDA receptor autoimmunity includes the characteristic delta brush-like waves, unmatched oligoclonal bands and temporal association between antibody and affective status. Possible mechanisms by which HSV infection could cause neuronal autoimmunity include a) limbic damage leading to exposure of NMDA receptor epitopes triggering a

second immune response and b) molecular mimicry. An alternative explanation is that the patient's neuropsychiatric symptoms emerged as a sequel to structural damage from HSV infection and the autoantibodies reflect an epiphenomenon, although this would not account for the delayed and transient nature of the manic episode.

Leypoldt et al. (2013) reported a case of NMDARE following HSVE, who presented with predominantly manic symptoms, and who recovered with steroid treatment. Notably, our patient did not receive immunotherapy, but recovered as serum anti-NMDA receptor antibodies became undetectable. The incidence of psychosis and mania is greatly increased following encephalitis (Granerod et al., 2017). Mechanisms underlying the development of postencephalitic psychiatric disorders are likely to be heterogeneous, however we suggest CNS autoimmunity should be considered a potential aetiological factor.

Within psychiatry, there has been recent interest in the role of NMDA receptor autoimmunity in 'primary' psychiatric disorders (Al-Diwani et al., 2017); specifically a temporal association between NMDAR (NR2) autoimmunity and mania has been reported in the context of bipolar disorder (Dickerson et al., 2012). It is notable that evidence of HSV infection in bipolar affective disorder is associated with poor cognitive function (Dickerson et al., 2004). Future research is indicated to explore whether NMDA receptor autoimmunity may be a mechanistic 'missing link' connecting HSV infection and cognitive/affective symptoms in psychiatric disorders, including bipolar affective disorder.

This case suggests that patients developing mood symptoms, and in particular mania, following HSV encephalitis should be investigated with NMDA receptor autoantibody testing.

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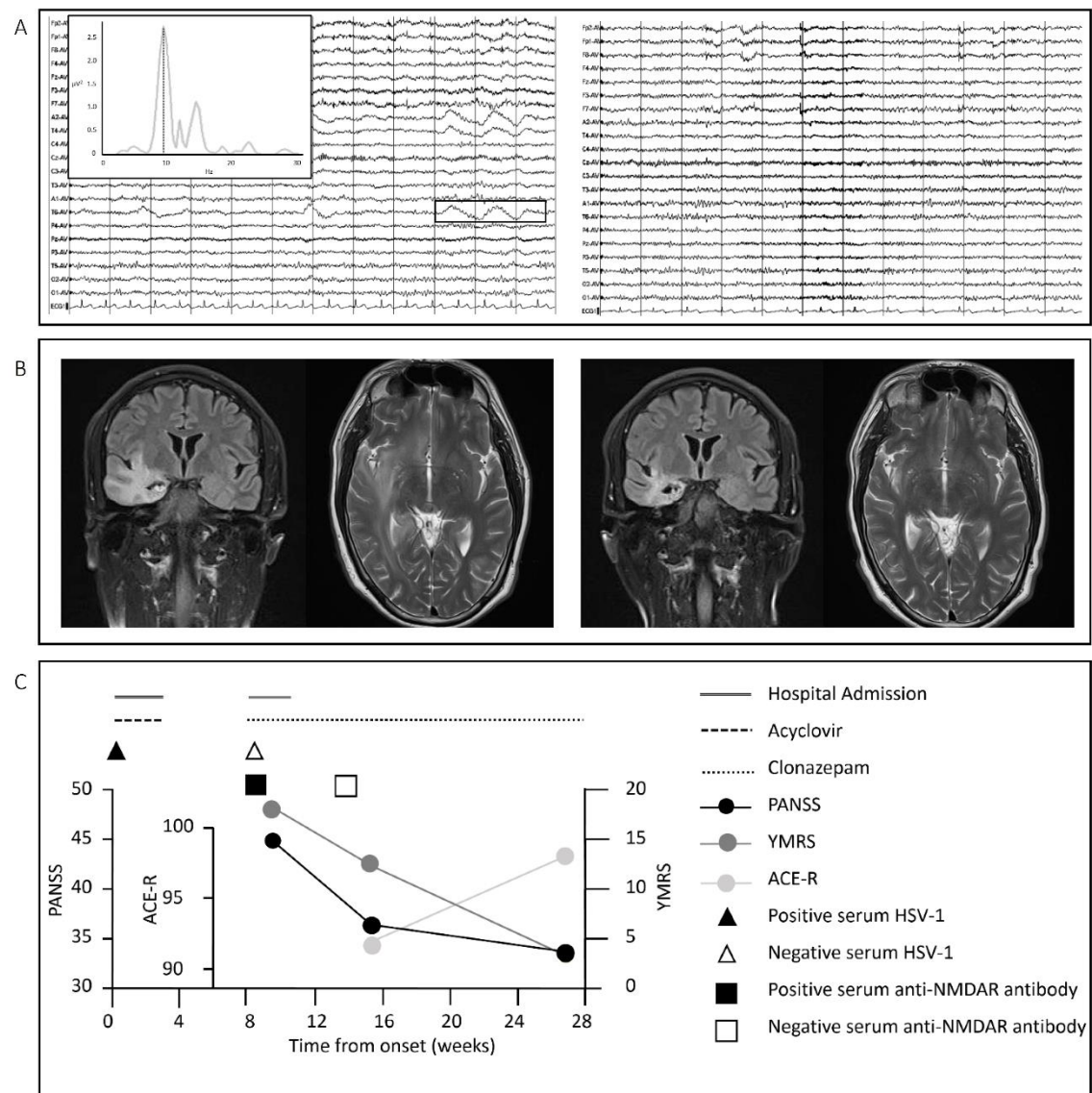


Figure 1: EEG and MRI on day five of admission (left) and at follow up (right) with time course of events. A) EEG showing dominant posterior reactive alpha background rhythm at 10-11 Hz. In addition there are frequent runs of right temporal delta waves, with superimposed serrated activity in the alpha and beta range of delta-brush like appearance which resolved at follow-up 24 weeks later. Spectral analysis over highlighted segment demonstrating power predominantly in the beta, alpha and delta frequency bands. B) Coronal Fluid Attenuation Inversion Recovery Sequences (FLAIR) and axial T2 showing initial swelling and signal hyperintensity within the right temporal lobe which reduced

at follow-up 15 weeks later, with persisting chronic encephalomalacia in the anterior right temporal lobe. C) Timeline of events from initial presentation including hospital admission, treatment, Herpes Simplex Virus (HSV) and anti-N-methyl-D-aspartate receptor (NMDAR) antibody status. Also plotted are total Positive and Negative Symptom Scale (PANSS), Young Mania Rating Scale (YMRS), and Addenbrooke's Cognitive Examination-Revised (ACE-R) scores.

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